Notice of Allowability	Application No.	Applicant(s)	
	09/936,602	OVERGAARD ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *October 17, 2005*.

2. ☒ The allowed claim(s) is/are *36*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Applicant's Request for Continuing Examination and response of October 17, 2005, to the Final Rejection of this case mailed May 18, 2005, is acknowledged. It is acknowledged that no claims have been amended, canceled, or added. Claim 36 is pending and is hereby reconsidered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claim 36 under 35 U.S.C. 103(a) as being unpatentable over Bersinger et al, 1984 in view of Epstein et al, 1992, Harlow and Lane, 1988, and Oxvig et al, 1993, as described in the prior actions, is withdrawn.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. The Oxvig et al reference does not teach or suggest that PAPP-A can circulate in an uncomplexed form but, in fact, discloses that PAPP-A is in a disulfide-bound complex with the pro-form of major basic protein (proMBP). It is only in view of the present specification that one of ordinary skill in the art would understand that an uncomplexed form of

PAPP-A even exists (pg 6, lines 23-24 and pg 31, lines 19-30). Measurable PAPP-A protease activity in pregnancy serum results from the fraction of uncomplexed PAPP-A.

These arguments are found to be persuasive. It was not known, prior to filing of the instant application, that bound proMBP inhibits the protease activity of PAPP-A and that only circulating, unbound PAPP-A, which is a small percentage, is enzymatically active. Therefore, a person of ordinary skill in the art would not be motivated, at the time the instant application was filed, to make an antibody that recognizes free PAPP-A but not PAPP-A complexed with proMBP.

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Title

Replace the title with:

–A method for detecting IGFBP-4 protease without detecting IGFBP-4 protease/proMBP complex–

Specification

Insert the following on page 1, line 2, after the title:

–This application is a US §371 filing of PCT/US00/06728, filed March 15, 2000 and published as WO 00/54806 on September 21, 2000, and claims the benefit of provisional application US 60/124,541, filed March 15, 1999, which expired September 21, 2001.–

Claims

For Claim 36, line 1, line 2, and twice on line 3, replace –PAPP-A– with –human PAPP-A–.

Authorization for this examiner's amendment was given in a telephonic interview with Monica McCormick Graham on November 9, 2005.

Allowable Subject Matter

Claim 36 is allowed.

The following is an examiner's statement of reasons for allowance:

The elected claim, Claim 36, is limited to a method for detecting human PAPP-A using an antibody that recognizes PAPP-A but not the PAPP-A/proMBP complex. The recited method has a specific, substantial, and credible patentable utility, based on the following.

Applicants have asserted that the utility for the recited method is in screening for growth-promoting or growth-inhibiting states (pg 1, parg 4). Such an assertion is credible as follows. The insulin-like growth factor (IGF) system includes the IGFI and IGFII growth factors, IGF-binding proteins (IGFBPs), and proteases that cleave the IGFBPs (for review see Mazerbourg et al, 2003). The instant specification discloses that the glycoprotein pregnancy-associated plasma protein-A (PAPP-A) is the same protein as IGFBP-4 protease (Example 1; especially pg 19). IGFBP-4 is known to sequester the growth factors IGFI and IGFII, while degradation of IGFBP-4 by IGFBP-4 protease, i.e. PAPP-A, leads to an increase in the bioavailability of IGFs (Mazerbourg et al, 2003; pg 247, parg 1 & pg 248, parg1). It is known that IGFs are important for growth-promoting states, including ovarian follicular development (Mazerbourg et al, 2003) and bone formation (Govoni et al, 2005 and Mohan et al, 1996). Thus, an immunological

method for measuring enzymatically active PAPP-A, as recited in the elected claim, is an efficient means to detect activation of the IGF growth factor system, a growth-promoting state.

It was known in the art, at the time the instant application was filed, that serum levels of PAPP-A are very high during third trimester pregnancy and that circulating PAPP-A is bound in a disulfide-bridged complex with proMBP (Oxvig et al, 1993). The specification teaches, for the first time, that proMBP is a bound inhibitor of PAPP-A protease activity; free, recombinant PAPP-A has 100-fold higher activity than PAPP-A/proMBP isolated from pregnancy serum (Example 4; especially pg 30, parg 5 – pg 31, parg 2). Based on the instant disclosure, one of skill in the art would believe, as asserted by Applicants, that more likely than not, the unbound form of circulating PAPP-A is the active form. Antibodies that recognize free PAPP-A but not the PAPP-A/proMBP complex were not known in the art and, in fact, Oxvig et al teach that commercially available polyclonal anti-PAPP-A antibodies are polyspecific, also reacting with MBP (Abstract). Antibodies to free IGFBP-4 protease were also not known. Thus, there was a need in the art for the development of antibodies to be used in an immunological method of detecting free, enzymatically active PAPP-A without detecting the PAPP-A/proMBP complex.

The instant specification is enabled. The human PAPP-A polypeptide, as well as the encoding nucleic acid sequence, were known in the art (Kristensen et al, 1994; IDS). With an appropriate antibody, standard immunological methods could easily detect free human PAPP-A without detecting the human PAPP-A/proMBP complex. The specification teaches methods for making such antibodies (pg 8, parg 3 – pg 9, parg 1). In fact, methods of reverse immuno-affinity purification, comprising adsorbing unwanted antibodies to antigens coupled to a solid phase, are well known in the art (Epstein et al, 1992). Thus, the method is enabled.

For these reasons, the elected invention has a specific, substantial, and credible patentable utility.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.

Art Unit 1656

SHERIDAN SWOPE, Ph.D.
PATENT EXAMINER